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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/802,162	GETTS, ROBERT	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on September 11, 2008 is acknowledged and has been entered. Claims 1-42 are pending.

Claims 1-42 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

Previous Rejections

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/187681, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, for claims 28, 30, 32 and 34, the prior filed provisional application does not disclose the use of at least three different capture sequences as part of multiple channel analysis. Instead, the specification of the prior filed application only makes reference to "3DNA™ expression array reagents are available with either Cy3™ or Cy5™ attached to the 3DNA™ molecule, making possible either single or dual channel detection in array experiments" (p. 1 of prior filed application). Therefore, due to the failure to provide adequate support for these claims, as currently amended, claims 28, 30, 32 and 34 are being afforded the effective filing date of the instant application, filed March 8, 2001.

Claim Rejections - 35 USC § 103

1. Claims 1-2, 5, 7-11, 13, 18, 20-22 and 35-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN 5, 487,973; January 1996). Sampson teaches a method for the amplification of the signal of target sequences using a bidirectional primer and cDNA synthesis (Abstract).

With regard to claim 1, Sampson teaches a method for detection and assay on a microarray, comprising:

a) taking a microarray having thereon a plurality of features each comprising a first particular first nucleotide sequence (p. 9, lines 28 to p. 10, line 3, where tagged cDNA is hybridized to the surface of an array; p. 1, lines 10-15, p. 7, lines 19-23 and p. 16, lines 16-18, where the type of array is described as comprising nucleic acid),

b) taking a first component comprising cDNA reagents having a capture sequence (Figure 1, where cDNA is generated that comprises a 3' sequence that provides a 'capture' sequence; p. 9 lines 4-26, specifically steps 1 and 2, where the target mRNA is transcribed into cDNA using a bidirectional primer); and

c) wherein said cDNA reagents comprise a plurality of different nucleotide sequences, and wherein said capture sequence of cDNA reagents is a common sequence among said cDNA reagents, said common sequence being complementary to the nucleotide sequence of said aptamer or signal amplification unit (Figure 1, where the bidirectional primer comprises a sequence that is common to all cDNA targets and which is complementary to the circular probe which generates a repeated signal amplification sequence with fluorescent labels or, see p. 11, lines 21-22, where it is contemplated that second half of the bidirectional primer is an aptamer for the purpose of generating signal amplification of the target w/ the aptamer attached; or see p. 16, lines 7-10, where signal amplification may be achieved by hybridizing a fluorescently tagged probe to the defined sequence added by the bidirectional primer);

d) mixing said first and second components at a temperature and for a time sufficient to enable said first component to bind to said second component (Figure 1, step 2, where the cDNA reagent is combined with a second component); and

e) incubating this mixture with said microarray to enable the first nucleotide sequences to bind to said first component, wherein said binding results in the generation of a hybridization pattern on the microarray (p. 9, lines 28 to p. 10, line 9, where tagged cDNA is hybridized to the surface of an array and the signal generated is detected);

f) wherein said first component comprising cDNA reagent is simultaneously hybridized to both said microarray and to said second component, while said first component comprising cDNA is on said microarray (Figure 1, step 2, where the cDNA reagent is combined with a second component; p. 9, lines 28 to p. 10, line 9, where tagged cDNA is hybridized to the surface of an array and the signal generated is detected).

With regard to claim 2, Sampson teaches the method of claim 1, wherein said cDNA reagents are obtained from mRNA of a target sample and further comprising the step of forming the first component comprising the cDNA reagent by contacting the mRNA with a quantity of a RT primer having the capture sequence, and with a reverse transcriptase, and nucleotide under conditions sufficient for initiating reverse transcription of the mRNA into said cDNA reagents (Figure 1, where cDNA is generated that comprises a 3' sequence that provides a 'capture' sequence; p. 9 lines 4-26, specifically steps 1 and 2, where the target mRNA is transcribed into cDNA using a bidirectional primer).

With regard to claim 10, Sampson teaches an embodiment of claim 1, further comprising scanning the microarray for detecting the detectable signal and the hybridization pattern generated (p. 9, lines 28 to p. 10, line 9, where tagged cDNA is hybridized to the surface of an array and the signal generated is detected).

With regard to claim 18, Sampson teaches a method for detection and assay on a microarray, said method comprising the steps of:

1) incubating a mixture including:

a first component comprising cDNA reagents having capture sequence (Figure 1, where the bidirectional primer comprises a sequence that is common to all cDNA targets and which is

complementary to the circular probe which generates a repeated signal amplification sequence with fluorescent labels or, see p. 11, lines 21-22, where it is contemplated that second half of the bidirectional primer is an aptamer for the purpose of generating signal amplification of the target w/ the aptamer attached; or see p. 16, lines 7-10, where signal amplification may be achieved by hybridizing a fluorescently tagged probe to the defined sequence added by the bidirectional primer); and

a second component comprising an aptamer/signal amplification region having a second nucleotide sequence (Figure 1, step 2, where the cDNA reagent is combined with a second component, wherein this component is depicted as a circular probe which generates a repeated signal amplification sequence with fluorescent labels; p. 11, lines 21-22, it is also contemplated that the signal amplification is generated through contact with an aptamer; or see p. 16, lines 7-10, where signal amplification may be achieved by hybridizing a fluorescently tagged probe to the defined sequence added by the bidirectional primer);

wherein said cDNA reagents comprise a plurality of different nucleotide sequence and wherein said capture sequence of said cDNA reagents is a common sequence among said cDNA reagents, said common sequence being complementary to said second nucleotide sequence of said aptamer, said capture sequence being used for binding said aptamers/signal amplification regions to said cDNA reagents (Figure 1, where the bidirectional primer comprises a sequence that is common to all cDNA targets and which is complementary to the circular probe or, see p. 11, lines 21-22, where it is contemplated that second half of the bidirectional primer is an aptamer for the purpose of generating signal amplification of the target w/ the aptamer attached; or see p.

16, lines 7-10, where signal amplification may be achieved by hybridizing a fluorescently tagged probe to the defined sequence added by the bidirectional primer);

2) contacting a microarray having thereon a plurality of features each comprising a particular first nucleotide sequence with said mixture (p. 9, lines 28 to p. 10, line 9, where tagged cDNA is hybridized to the surface of an array and the signal generated is detected); and

3) incubating said microarray and said prehybridized cDNA-signal amplification complex at a second temperature and for a time sufficient to induce said prehybridized cDNA-aptamer/signal amplification complex to bind to said first nucleotide sequence, wherein such binding results in the generation of a hybridization pattern on said microarray (p. 9, lines 28 to p. 10, line 9, where tagged cDNA is hybridized to the surface of an array and the signal generated is detected).

With regard to claim 20, Sampson teaches an embodiment of claim 1, wherein said mixing of said first and second components is conducted on said microarray (p. 10, lines 10-16, where the order of steps can be varied and may included hybridization of the 1st and second components before hybridization to the array, or after).

With regard to claim 21, Sampson teaches an embodiment of claim 1, wherein said mixing of said first and second components is conducted off of said microarray (p. 10, lines 10-16, where the order of steps can be varied and may included hybridization of the 1st and second components before hybridization to the array, or after).

With regard to claim 22, Sampson teaches an embodiment of claim 18, wherein said cDNA reagents are obtained from mRNA of a target sample and further comprising the step of forming the first component comprising the cDNA reagents by contacting the mRNA with a quantity of a RT primer having the capture sequence and with a reverse transcriptase, and

nucleotide under conditions sufficient for initiating reverse transcription of the mRNA into cDNA reagents (Figure 1, where cDNA is generated that comprises a 3' sequence that provides a 'capture' sequence; p. 9 lines 4-26, specifically steps 1 and 2, where the target mRNA is transcribed into cDNA using a bidirectional primer).

With regard to claim 35 and 37, Sampson teaches an embodiment of claim 1 and 18, wherein said capture sequence comprises more than one type of base (p. 9, lines 23-26).

With regard to claim 36 and 38, Sampson teaches an embodiment of claim 1 and 18, wherein said capture sequence comprises adenine, guanine, cytosine and thymine bases (p. 9, lines 23-26).

With regard to claim 39-40, Sampson teaches an embodiment of claim 1 and 18, wherein said method is used for expression analysis (p. 1, lines 12-15, where arrays are useful for expression analysis).

Regarding claim 1-2, 18 and 41-42, Sampson does not teach use of dendrimer nucleotide sequences comprising at least one first arm comprising a label and at least one second arm having a second nucleotide sequence, or that the second component comprises a dendrimer nucleotide sequence. Furthermore, while Sampson teaches microarray formats for detection, Sampson does not teach detection of dendrimers bound to an array. Nilsen teaches detection of nucleic acids using dendrimeric probes (Abstract).

Regarding claims 1-2, 18 and 41-42, for detecting a specific nucleic acid in a target sample using a dendrimeric probe wherein Nilsen et al. teach that the method comprises (i) contacting a bead having specific probe sequences with a mixture containing a first component comprising labeled target nucleic acid (DNA or RNA) having a capture sequence and a second

component comprising a dendrimer having at least one arm with a nucleotide sequence complementary to the capture sequence of the first component (see column 14, lines 30-35, column 15, lines 37-63); (ii) mixing the first and second components at a temperature to form a bridge between the two components to enable the cross-linking of first component to the second (see column 16, lines 8-11); and incubating the bound mixture with the microarray and detecting signal as an indication of the binding of the target sequence to the specific probe sequence on the bead (see column 16, lines 12-67, column 18, lines 27-51).

With regard to claim 5 and 9, Nilsen teaches an embodiment of claim 1, wherein the temperature sufficient to enable the second component to bind to the first component is from about 50 to about 55°C (col. 20, lines 24-44, where the components including the dendrimers bind for 37oC, which is about 50°C), and wherein the microarray and the mixture are incubated overnight at the temperature from about 42 to 65°C in a humidified chamber (col. 20, lines 24-44, where the components including the dendrimers bind for 37oC, which is about 42°C).

With regard to claim 7-8, Nilsen teach that the method comprises annealing times ranging from 8 minutes (see column 20, lines 24-44) to overnight (see column 3, lines 49-60).

With regard to claim 10, Nilsen teaches an embodiment of claim 1, further comprising scanning the microarray for detection of hybridization pattern includes detecting the detectable signal (see column 20, lines 38-40).

With regard to claim 11, Nilsen teaches an embodiment of claim 1, further comprising washing the microarray to purge dendrimers unattached to the microarray after the incubation of the microarray and the mixture (see column 20, lines 35-37).

With regard to claim 13, Nilsen teaches an embodiment of claim 1, wherein the method comprises hybridization buffer (see column 19, lines 14-26; col. 20, lines 60-64, where the hybridization buffer comprises the components of NaPO4, EDTA and SSC).

Furthermore, while Nilsen doesn't teach the same concentrations of components of the wash buffer as claimed, Nilsen states that the conditions can be varied and an ordinary practitioner would have recognized that the results optimizable variables of time, product amount and buffer component elements and concentrations could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific wash buffer was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Furthermore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method of microarray hybridization with signal amplification taught by Sampson to incorporate the method for detecting a nucleic acid sequence using a dendrimer sequence as taught by Nilsen et al. to arrive at the claimed invention with a reasonable expectation for success. Nilsen et al. states that "background noise could be generated in conventional assay not only from binding to a solid support, but also from binding of the probe to nonhomologous DNA sequences. An open branching of a dendrimeric DNA have many degrees of freedom in their movement relative to each other and have a high avidity

for DNA that is complementary to the non-annealed single stranded sequences (see column 18, lines 14-26, column 7, lines 14-19). Furthermore, the method taught by Sampson is directed specifically to "a method of amplifying the signal of a target nucleic acid sequence" (p. 4, lines 27-28) and Sampson also teaches "the method of the invention may be used to generate a defined repeated DNA sequence containing only the four naturally-occurring bases where signal amplification may be achieved by hybridizing a fluorescently tagged probe to this defined sequence" (p. 16, lines 6-15). Therefore, the two methods are directed to different but related methods of achieving signal amplification of target nucleic acid sequences using fluorescence and an ordinary practitioner would have been motivated to adjust the method of Sampson to include the dendrimeric probe as taught by Nilsen et al. in order to achieve the expected advantage of developing a sensitive method for detecting a target nucleic acid with a reasonable expectation for success.

2. Claims 3-4, 16-17, 19 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN. 5, 487,973; January 1996) as applied to claims 1-2, 5, 7-15, 18-22 and 35-42 above, and further in view of Combates et al. (US Patent 6,045,998; April 2000).

With regard to claim 16-17 and 25-26, Nilsen teaches an embodiment of claim 3 and 23, wherein the purging step further comprises the use of a hybridization chamber or station (col. 20, lines 20-33).

However, neither Nilsen nor Sampson teaches the use of a spin column to remove unhybridized RT primer. Combates teaches the exclusion of excess RT primer prior to the use of cDNA in downstream applications.

With regard to claim 3 and 23, Combates teaches an embodiment of claim 2 and 22 further comprising the step of purging excess unhybridized RT primer from said first component prior to incubation of said mixture (col. 9, lines 33-38, where excess oligo-d(T), which is used as an RT primer at col. 9, lines 1-4, is removed by chromatography on a spin column).

With regard to claim 4, 19 and 24, Combates teaches an embodiment of claim 3 and 23, wherein the purging step further comprises the step of passing the first component through a spin column media to remove excess RT primer (col. 9, lines 33-38, where excess oligo-d(T), which is used as an RT primer at col. 9, lines 1-4, is removed by chromatography on a spin column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Sampson to incorporate the step of removing excess reverse transcriptase primer as taught by Combates to arrive at the claimed invention with a reasonable expectation for success. As taught by Combates, "contaminating oligo(dT) primer was removed by chromatography on a spin column" (col. 9, lines 33-38) prior to further downstream processing including amplification of the cDNA and electrophoresis. Therefore, considering the teachings of Combates where excess RT primer was removed prior to further analysis of the synthesized cDNA and considering the focal role the bifunctional RT primer plays in the method taught by Sampson in view of Nilsen, one of ordinary skill in the art at the time the invention was made would have been motivated to include the step of RT primer

removal taught by Combates into the method of signal amplification taught by Sampson and Nilsen to arrive at the claimed invention with a reasonable expectation for success.

3. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN 5, 487,973; January 1996) as applied to claims 1-2, 5, 7-11, 13, 18, 20-22 and 35-42 above, and further in view of Kool et al. (US Patent 5,714,320; February 1998). Sampson teaches a method for the amplification of the signal of target sequences using a bidirectional primer and cDNA synthesis (Abstract).

Sampson in view of Nilsen teach all of the limitations of claims 1-2, 5, 7-11, 13, 18, 20-22 and 35-42 as recited in the rejection stated above. However, while Sampson teaches hybridization of the second end of the bidirectional primer to the circular signal amplifying template (Figure 1, p. 9, lines 15-17), Sampson does not specify the hybridization temperature. Kool teaches hybridization of a nucleic acid probe with a circular nucleic acid (Abstract).

With regard to claim 6, Kool teaches an embodiment of claim 1, wherein the temperature sufficient to enable the first component to bind to the first nucleotide sequence is from 42 to 65^{o}C (col. 13, lines 13-22, where the temperature of the reaction mixture during rolling circle is about 20-90 ^{o}C).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the specific hybridization temperature taught by Kool to the method taught by Sampson in view of Nilsen to arrive at the claimed invention with a reasonable expectation for success. While Sampson does not teach specific hybridization temperatures, one of ordinary skill in the art would have looked to the prior art for guidance regarding specific and

suitable hybridization temperatures. Sampson teaches that circular templates useful in the method comprise rolling circle probes. Kool teaches "the preferred reaction time for rolling circle synthesis is about 1 hour to about 3 days. Preferrably, the temperature of the reaction mixture during the rolling circle synthesis is about 20-90 °C" (col. 13, lines 13-22). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the specific hybridization temperature taught by Kool for hybridization and extension of circular templates to the method taught by Sampson in view of Nilsen to arrive at the claimed invention with a reasonable expectation for success.

4. Claim 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN 5, 487,973; January 1996) as applied to claims 1-2, 5, 7-11, 13, 18, 20-22 and 35-42 above, and further in view of Wang et al. (US Patent 6,004,775; December 1999). Sampson teaches a method for the amplification of the signal of target sequences using a bidirectional primer and cDNA synthesis (Abstract).

Sampson in view of Nilsen teaches all of the limitations of claims 1-2, 5, 7-11, 13, 18, 20-22 and 35-42 as recited in the rejection above.

With regard to claim 13-15, Nilsen teaches an embodiment of claim 1, wherein the method comprises hybridization buffer (see column 19, lines 14-26), wherein the hybridization buffer comprises 0.25 M NaPO4, 4.5% SDS, 1 mM EDTA, and 1X SSC (col. 20, lines 60-64, where the hybridization buffer comprises the components of NaPO4, EDTA and SSC).

However, regarding claim 12, Nilsen does not specifically teach the washing step as comprising specific concentrations of SSC buffers. Regarding claim 14, Nilsen does not specifically teach that the hybridization buffer comprises SDS or additional components. Wang teaches methods of quantitative gene expression analysis using microarrays (Abstract).

With regard to claim 12, Wang teaches an embodiment of claim 11, wherein the washing step further comprises:

a) washing the microarray with 2X SSC buffer containing 0.2% SDS at 55oC for about 10 minutes; b) washing the microarray with 2X SSC buffer at about room temperature for about 10 minutes; and c) washing the microarray with 0.2X SSC buffer at about room temperature for about 10 minutes (col. 10, lines 40-55, where the slides were washed with concentrations of SSC for different incubation times and temperatures).

With regard to claim 13-15, Wang in view of Nilsen teaches an embodiment of claim 1, wherein the method comprises hybridization buffer (col. 10, lines 25-41; col. 6, lines 18-22), wherein the hybridization buffer comprises 4.5% SDS and 1X SSC (col. 10, lines 25-41, where the hybridization buffer comprises 5X SSC and 1% SDS) and further comprises 40% formamide, 4X SSC, and 1% SDS (col. 10, lines 25-41, where the hybridization buffer comprises 5X SSC and 1% SDS; col. 6, lines 18-22).

Furthermore, while Wang, Nilsen and Sampson don't teach the same concentrations of components of the wash buffer or exact hybridization temperatures as claimed, Wang states that the conditions can be varied and an ordinary practitioner would have recognized that the results optimizable variables of time, product amount and buffer component elements and

concentrations could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific wash buffer was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Sampson and Nilsen, which refer generally to array formats to include the specific washing times and wash buffer compositions of Nilsen in view of Wang to arrive at the claimed invention with a reasonable expectation for success. As taught by Wang, "suitable hybridization conditions are well known to those of skill in the art and reviewed in Maniatis et al, supra, and WO95/21944, where the conditions can be modulated to achieve a desired specificity in hybridization, e.g., highly stringent or moderately stringent conditions" (col. 6, lines 10-22). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Sampson and Nilsen, which refer generally to array formats to include the specific washing times and wash buffer compositions of Nilsen in view of Wang to arrive at the claimed invention with a reasonable expectation for success.

5. Claims 27-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN. 5, 487,973; January 1996) as applied to claims 1-2, 5-15, 18-22 and 35-42 above, and further in view of Brenner et al. (US Patent 5,846,719; December 1998).

With regard to claims 27-34, Sampson teaches a method which comprises dual or multi-channel analysis and wherein the method comprises reverse transcription into cDNA (p. 10, lines 6-9, where the tags incorporated into the signal amplification sequence are fluorescent moieties that may be detected by monitoring the fluorescence emission at defined sets or ranges of wavelengths; see Figure 1, where mRNA is reverse transcribed into cDNA).

With regard to claim 27, 29, 31 and 33, Brenner teaches an embodiment of claim 1-2, 18 and 22, such that said analysis uses two different capture sequences (col. 11, line 61 to col. 12, line 20, where oligonucleotide tags preferably range in length from 18-40 nucleotides and preferably contain at least 100 members, which is more than 2 different capture sequences).

With regard to claim 28, 30, 32 and 34, Brenner teaches an embodiment of claim 1-2, 18 and 22, such that said analysis uses at least three different capture sequences (col. 11, line 61 to col. 12, line 20, where oligonucleotide tags preferably range in length from 18-40 nucleotides and preferably contain at least 100 members, which is more than 3 different capture sequences).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporate the multitude of oligonucleotide tags taught by Brenner into the method of signal amplification taught by Sampson and Nilsen to arrive at the claimed invention with a reasonable expectation for success. Brenner addresses a need in the art by providing, "an oligonucleotide-based tagging system which provided a large repertoire or tags,

but which also minimized the occurrence of false positive and false negative signals without the need to employ special reagents for altering natural base pairing and base stacking free energy differences. Such a tagging system would find applications in many areas, including construction and use of combinatorial chemical libraries, large-scale mapping and sequencing of DNA, genetic identification, medical diagnostics and the like". Brenner also teaches how this variety of oligonucleotide tags, may be synthesized, including "oligonucleotide tags of the invention are synthesized combinatorially out of subunits between three and six nucleotides in length and selected from the same minimally cross-hybridizing set" (col. 8, lines 50-53). Finally, Brenner notes that "the invention provides a method of labeling and sorting molecules, particularly polynucleotides by the use of oligonucleotide tags" (col. 7, lines 42-44). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to adjust the method taught by Sampson and Nilsen to incorporate the variety of additional oligonucleotide tag sequences taught by Brenner into the primer sequence to arrive at the claimed invention with a reasonable expectation for success.

Response to arguments

Applicant's arguments filed September 11, 2008 have been fully considered but they are not persuasive.

Applicant asserts that the previous office action don't traverse the remarks submitted in the prior response. Applicant asserts that the prior response amended claim 1 to require simultaneous hybridization and that Sampson does not teach simultaneous hybridization (p. 13 of remarks).

Applicant also reiterate the remarks from the prior response and assert that "the remarks regarding the very disparate methods of Sampson and Nilsen (with respect to Sampson's use of covalent bonding and so forth) also do not appear to be addressed by the office action" (p. 14 of remarks).

These arguments have been considered but are not persuasive. Applicant argues regarding Sampson that "Sampson discloses hybridization to the surface of the solid substrate as a separate step from step 2, which he refers to as optional step 5". Applicant goes on to quote a passage in Sampson which states "some applications may dictate that the signal amplification sequence be polymerized onto the target sequence subsequent to hybridization onto the surface-bound probe giving an overall step order of: (1), (2), (5), (3), (4), (6)".

While these arguments are noted, these arguments are not persuasive. First, it is noted that it appears that applicant is interpreting the term simultaneous in a different way than the term is claimed. Regarding simultaneous, the claim states "wherein said first component comprising cDNA reagents is simultaneously hybridized to both said microarray and to said second component comprising dendrimer, while said first component comprising cDNA is on said microarray". That Sampson achieves this simultaneous hybridization using multiple steps is irrelevant. As long as Sampson achieves simultaneous hybridization between a first component (cDNA), a second component (dendrimer) and the microarray, then the claimed invention is obvious over Sampson in view of Nilsen, regardless of the number of steps used to achieve the end result. It is also noted that Applicant cites the passage as a teaching away, when it is clearly another alternative embodiment envisioned by the reference. The reference states an original order of 1, 2, 3, 4, (optional), 5 and 6. The reference also states "the method of the invention is

not strictly limited to the order of steps set forth above" and goes on to teach alternative embodiments, including where steps 3 and 4 precede steps 1 and 2, and also the embodiment cited by Applicant. While this teaching is noted, it is not viewed as a teaching away from the invention as recited in the rejection and argued further below.

Sampson teaches in Figure 2 and page 9, that cDNA (component 1) is hybridized to a bidirectional primer, polymerized, a second component is added which yields a signal amplification element in the form of tags (component 2). Step 5 of page 9 states "the tagged cDNA is hybridized to the surface of a solid substrate, such as an array or a microscopic bead. The hybridization conditions must not disrupt the secondary structure of the repeating signal amplification sequence which contributes to its detectability". Therefore, the optional step 5 achieves simultaneous hybridization of the cDNA to the array and to the "tagged" signal generation element. Furthermore, the final step of Figure 2, in fact, depicts a cDNA that is simultaneously hybridized to an array, and to the second component simultaneously. While the tagged element on the second arm of Sampson does not explicitly comprise the dendrimer as claimed, this element is taught in combination with Nilsen. Therefore, Applicant's arguments are not persuasive.

In response to Applicant's assertion that remarks regarding Sampson's use of covalent bonding were not addressed in the previous office action, this assertion is not correct. Applicant's attention is pointed to the remarks in the previous office action, starting at page 19 and particularly at page 20, where this issue is addressed. Therefore Applicant's arguments are not persuasive and the rejections are maintained.

The remaining rejections are maintained for the reasons made of record in the rejections above and in view of the arguments made of record in the previous office action.

Relevant Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Wolber et al. (US Patent 6,235,483; May 2001) discloses methods and kits for labeling nucleic acids using tagged oligonucleotides (Abstract).

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephanie K. Mummert/
Examiner, Art Unit 1637

/Teresa E Strzelecka/

Primary Examiner, Art Unit 1637

January 4, 2009